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Bias due to Selection on Live Births in Studies of Environmental Exposures during Pregnancy: A Simulation Study

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Background: Studies of the effects of prenatal environmental exposures on postnatal outcomes are particularly vulnerable to live birth bias; i.e., the bias that arises from the necessary restriction of the analysis to live births when that is influenced by both the exposure under study *A* and unmeasured factors *U* that also affect the outcome.

Objectives: In the context of a recent publication of nitrogen dioxide (NO_2) and autism spectrum disorder (ASD) that found an odds ratio (OR) of 0.77 per 5.85 ppb NO_2 during pregnancy, we aimed to examine what parameters would be needed to account for this protective association through live birth bias.

Methods: We simulated the magnitude of bias under two selection mechanisms and when both mechanisms co-occur, assuming a true null effect. Simulation input parameters were based on characteristics of the original study and a range of plausible values for the prevalence of unmeasured factor *U* and the ORs for the selection effects (i.e., the effects of NO_2 and *U* on loss and of *U* on ASD). Each scenario was simulated 1,000 times.

Results: We found that the magnitude of bias was small when NO_2 and *U* independently influenced pregnancy loss (collider-stratification without interaction), was stronger when NO_2-induced loss preferentially occurred in $U = 1$ (depletion of susceptibles), and was strongest when both mechanisms worked together. For example, ORs of 3.0 for NO_2-loss, *U*-loss, *U*-ASD, and *U* prevalence = 0.75 yielded NO_2-ASD ORs per 5.85 ppb NO_2 of 0.95, 0.89, and 0.75 for the three scenarios, respectively. The bias is amplified with multiple *U*s, yielding ORs as low as 0.51.

Discussion: Our simulations illustrate that live birth bias may lead to exposure–outcome associations that are biased downward, where the extent of the bias depends on the fetal selection mechanism, the strength of that selection, and the prevalence of *U*. https://doi.org/10.1289/EHP7961

Introduction

Understanding the health effects of environmental exposures is critical for identifying and developing preventive interventions for high-risk populations. However, these effects may not be identifiable if exposure prevents selection into the study and thus, observation of the outcome of interest. This process is a form of 'left truncation' and can lead to estimates of exposure-outcome associations that are biased (Howards et al. 2007; Lisonkova and Joseph 2015). Epidemiological studies of environmental exposures are particularly vulnerable to left truncation as exposures are typically ubiquitous in time (e.g., participants are already exposed prior to study initiation), such that exposure-induced selection processes likely inform the formation of observational cohorts from which exposure-health effects are estimated.

In studies investigating the effects of prenatal exposures on outcomes in live-born children, left-truncation can induce a specific type of selection bias called live-birth bias (Liew et al. 2015a; Raz et al. 2018a). These studies are typically based on cohorts formed by only live births, where selective survival between conception and birth can skew the distribution of prenatal exposures in the subset available for analysis (i.e., those conceptions that resulted in a live birth) from the exposure distribution among all conceptions, such that the estimated parameter in the analyzed subset differs from the parameter in the total population (i.e., all conceptions).

An example of possible live-birth bias is a recent analysis of traffic-related nitrogen dioxide (NO_2) and autism spectrum disorder (ASD), where the odds ratio (OR) was 0.77 per 5.85 parts per billion (ppb) increase in NO_2 during pregnancy when mutually adjusted for postnatal exposure to NO_2 (Raz et al. 2018b); that is, prenatal exposure to NO_2 appeared to be protective against ASD. This paradoxical finding is unlikely to be causal because we are not aware of a possible biological mechanism for which NO_2 may confer beneficial effects on the risk of ASD, or for human health in general for that matter. It is more likely that this strong protective association could be attributed to live-birth bias.

It has been suggested that there are two selection mechanisms that can lead to live-birth bias (Liew et al. 2015a; Raz et al. 2018a). Although parameterized differently, both mechanisms can be envisioned as forms of collider-stratification bias (Hernan and Robins 2020) and can be represented by the directed acyclic graph (DAG) in Figure 1, which is the same structure as the birth weight paradox (Hernández-Díaz et al. 2006). We will refer to these mechanisms here as "collider-stratification without interaction" and "depletion of susceptibles." In "collider-stratification without interaction," exposure *A* and some unmeasured factor *U*—for example, exposure to endocrine disrupting chemicals that have been associated with pregnancy loss and autism (Jensen et al. 2015; Kalkbrenner et al. 2014; Krieg et al. 2016; Pelch et al. 2019)—are independent, and each affect selection (*S*). In "depletion of susceptibles," which is separate but related to the first mechanism, exposure *A* and unmeasured variable *U* do not have independent causal effects on fetal loss, but rather loss is dependent on the joint effects of *A* and *U*. A potential example of this mechanism is a gene–environment interaction, whereby exposure-induced loss preferentially occurs in those who have the genetic factor *U* (i.e., the subset of fetuses susceptible to ASD). Last, both mechanisms described above can also work in

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tandem because they operate through distinct mechanistic pathways, in that A and U not only causally interact to affect fetal loss but also have independent causal effects on fetal loss. It is important to note that although the three mechanisms described above are parameterized differently, they are indistinguishable on a DAG because DAGs are nonparametric and thus cannot encode biases that depend on the specific parameterization of the effect. That is, they all represent the same causal structure (but are parameterized differently) where restricting the analysis to live births (i.e., conditioning on collider $S=1$) induces a spurious association between A and U, which results in a biased $A-Y$ association (Figure 1).

Unlike other examples of selection bias, such as the birth weight paradox (Hernández-Díaz et al. 2006), obesity paradox (Glymour and Vittinghoff 2014; Lajous et al. 2015; Sperrin et al. 2016), or loss to follow-up in cohort studies (Howe et al. 2016), live-birth bias is less amenable to addressing analytically because we cannot adjust for selection processes that we cannot observe (i.e., the necessary data to mitigate this bias are often not available). Thus, simulations are an invaluable tool for exploring the influence of live-birth bias on the estimation of the effects of exposure during pregnancy on outcomes in live-born children. Motivated by the findings of Raz et al. (2018b), we examine through simulations the magnitude of bias that would result from analyses under the two hypothetical selection mechanisms as well as when they operate simultaneously.

Methods

Data-Generating Process

To examine bias from selection on live births under a true null effect of NO_2 on ASD, we simulated a pregnancy cohort of 100,000 conceptions, which we will refer to as the "total population," with data on entire-pregnancy NO_2 exposure A, an unmeasured factor U, the ASD outcome Y, and selection indicator S (Figure 1). Entire-pregnancy NO_2 was normally distributed with mean 16.7 and standard deviation of 4.3 to reflect the distribution of NO_2 found in the original study (Raz et al. 2018b). For simplicity, we ignored the seasonal nature of the NO_2 exposure, and though we treated the exposure as Gaussian, the same principles would apply for a binary exposure. Unmeasured variable U and outcome Y were binary variables. The prevalence of U (π_U) was set to be 0.25, 0.50, or 0.75. The baseline odds of Y were set to be 0.015 to reflect the low incidence of ASD in the original analysis (Raz et al. 2018b), and the baseline odds of fetal loss were set to be 0.05, such that the causal effects that lead to selection bias [i.e., $A \rightarrow S$, $U \rightarrow S$, $\{AU\} \rightarrow S$ (i.e., the effect of the $A-U$ interaction), and $U \rightarrow Y$], which we will henceforth refer to as "selection effects," lead to an overall loss in line with observed estimates (Wilcox et al. 1988). All selection effects were modeled in terms of ORs, so that simulated probabilities were correctly bounded between 0 and 1; and for the $A \rightarrow S$, $U \rightarrow S$, $\{AU\} \rightarrow S$, and $U \rightarrow Y$ associations (OR_{AS}, OR_{US}, $OR_{\{AU\}S}$, OR_{UY}, respectively) that were not 1.0 as determined by the selection mechanism (see "Selection Mechanisms" section below) were set to all be the same and equal to 1.5, 2.0, 2.5, or 3.0 (for OR_{AS}, this is per 5.85 ppb increase in NO_2, the interquartile range in the original study). Here, we only considered effects of the same sign because exposures that are harmful for pregnancy loss are most likely also harmful for ASD (beneficial exposures would function in the same manner, in that what is beneficial for loss is also beneficial for ASD, whereas those of opposite signs that we considered less plausible would lead to upwardly biased $A-U$ and $A-Y$ associations among live births). For simplicity of displaying, we will refer to the selection effects ORs as OR_S henceforth. The probability of loss and the ASD outcome Y for each fetus i were estimated using the equations below. Equation 1 represents the probability that the pregnancy will result in a fetal loss given A and U. Equation 2 represents the probability of the outcome Y given U, where A is omitted because our simulations were conducted under the null; that is, there is no causal effect of A on Y.

$$P(loss_i) = \frac{\exp(\beta_0 + \beta_1 A_i + \beta_2 U_i + \beta_3 A_i * U_i)}{1 + \exp(\beta_0 + \beta_1 A_i + \beta_2 U_i + \beta_3 A_i * U_i).} \quad (1)$$

$$P(Y_i) = \frac{\exp(\gamma_0 + \gamma_1 U_i)}{1 + \exp(\gamma_0 + \gamma_1 U_i).} \quad (2)$$

Selection Mechanisms

To examine bias from collider-stratification with no interaction [Mechanism 1 (M1)], where both A and U have independent causal effects on fetal loss, selection effects were set to the OR_S specified above, except that $\exp(\beta_3) = OR_{\{AU\}S}$ was set to 1. For depletion of susceptibles [Mechanism 2 (M2)], $\exp(\beta_1) = OR_{AS}$ and $\exp(\beta_2) = OR_{US}$ were set to be 1, whereas $\exp(\beta_3) = OR_{\{AU\}S}$ was set equal to the prespecified OR_S; that is, A and U do not have independent causal effects on fetal loss and loss due to NO_2 could only occur in the subset of fetuses who were exposed to U. Finally, to examine bias from both mechanisms operating simultaneously (Both Mechanisms [M1+2]), where both A and U have independent causal effects on fetal loss and they causally interact on selection, $\exp(\beta_1) = OR_{AS}$, $\exp(\beta_2) = OR_{US}$ and $\exp(\beta_3) = OR_{\{AU\}S}$ were set to the specified OR_S. For all mechanisms, $OR_{UY} = \exp(\gamma_1)$ was set to the prespecified selection effect OR_S, such that the extent of the bias is driven by the differing parameterizations of the relations between A, U, and S across the three selection mechanisms (and not the $U-Y$ relationship, which is fixed to be constant for each scenario). To focus only on the bias induced by the selection effects, all simulations assumed that there was no confounding for the effect of NO_2, loss to follow-up among live-born children, outcome misclassification, or exposure misclassification, such that observed associations can only be explained by live-birth bias.

Analysis

Each scenario was simulated 1,000 times. For each simulated data set, we first restricted our analytic sample to live births (i.e., $S=1$) and then performed a logistic regression of ASD status in children with NO_2 exposure to obtain the observed odds ratio $OR_{AY|S=1}$ (per 5.85 ppb), which approximates the risk ratio because the outcome is rare. With the distribution of point

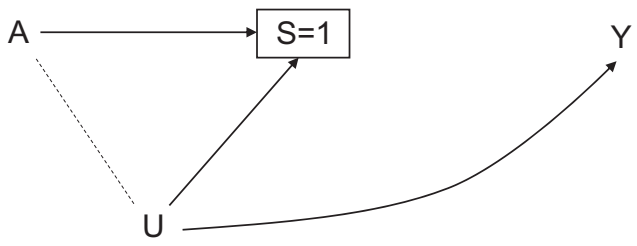

Figure 1. DAG of the structure of live birth bias. Nitrogen dioxide (NO_2) exposure A affects live births S is also affected by an independent unmeasured risk factor U for ASD (outcome Y). Arrows are direct causal effects, and the dashed line is a spurious association induced between A and U after selection on live births (i.e., conditioning on $S=1$). This DAG has the same structure as the birthweight paradox (Hernández-Díaz et al. 2006). Note: ASD, autism spectrum disorder; DAG, directed acyclic graph.

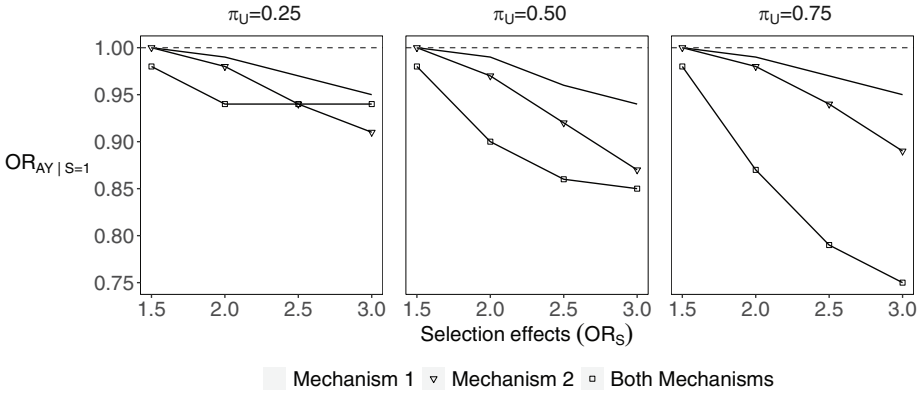

Figure 2. Live birth bias of OR_{AY} under different selection effects. Average odds ratios for the association between nitrogen dioxide (NO_2; exposure A) and ASD (outcome Y) among live births $S=1$ ($OR_{AY|S=1}$) with varying simulation inputs for the prevalence of the unmeasured risk factor U (π_U) and the magnitude of selection effects (OR_S) under two selection mechanisms (collider-stratification without interaction, and depletion of susceptibles) and when they both co-occur with a single U, assuming a true null effect of NO_2 on ASD. Collider-stratification without interaction (Mechanism 1) occurs when A and U have independent causal effects on fetal loss, but with no interaction on the multiplicative scale ($OR_{\{AU\}S}=1$, and $OR_{AS}=OR_{US}=OR_{UY}=OR_S$). Depletion of susceptibles (Mechanism 2) occurs when A has a causal effect on fetal loss only in the subset of susceptible fetuses ($U=1$), but neither A or U have independent causal effects on fetal loss ($OR_{AS}=OR_{US}=1$, and $OR_{\{AU\}S}=OR_{UY}=OR_S$). Both mechanisms occur when A and U have independent causal effects on fetal loss, and with interaction on the multiplicative scale ($OR_{AS}=OR_{US}=OR_{\{AU\}S}=OR_{UY}=OR_S$). Each scenario was simulated 1,000 times. Points represent the mean $OR_{AY|S=1}$ in each scenario. Dashed lines indicate the true null effect of NO_2 on ASD ($OR_{AY}=1$) in the absence of live birth bias, where deviations from 1.0 quantify the magnitude of live birth bias. See Table S1 for corresponding numeric data, including 95% SI. Note: ASD, autism spectrum disorder; OR, odds ratio; SI, simulation intervals.

estimates generated over the 1,000 iterations for each scenario, we computed the mean $OR_{AY|S=1}$ and percentile-based 95% simulation intervals (SIs), which are the 2.5th and 97.5th percentiles of the distribution. Because the simulated truth is that there is no causal effect, the value of $OR_{AY|S=1}$ demonstrates the bias ratio, where greater departures from 1 indicate larger magnitudes of bias. Furthermore, SIs demonstrate the range of $OR_{AY|S=1}$ estimates that are consistent with the data generating mechanism for the specified sample size; for example, if the 95% SIs generated by a given selection mechanism included the OR of 0.77 found in the original study (Raz et al. 2018b), it would suggest that this observed protective association would be consistent with live-birth bias induced by that mechanism.

To better understand the drivers of bias from the different selection mechanisms, we also estimated the OR for the association between A (NO_2 exposure, per 5.85 ppb) and U in the selected population ($OR_{AU|S=1}$) using a logistic regression, the prevalence of U in the selected population ($\pi_{U|S=1}$), and their respective 95% SIs. Because both parameters determine the strength of live-birth bias and are driven by the simulation inputs OR_S and π_U, we will henceforth refer to both parameters as "bias parameters." The simulation input OR_{AU} is expected to be 1 in the total population of all conceptions, but the parameter $OR_{AU|S=1}$ is expected to be below 1 in the selected population (i.e., fetuses that survived) because those exposed to both high air pollution A and U are strongly selected against, because both factors increase the likelihood of loss. Thus, those exposed to high air pollution in the selected population are less likely to be exposed to U (and vice versa) setting up an inverse association between A and U. Furthermore, the difference between $\pi_{U|S=1}$ and π_U indicates the extent to which the $U \rightarrow S$ and $A \rightarrow S$ determine the prevalence of U in those selected; that is, the expected value of $\pi_{U|S=1}$ is π_U in the absence of bias.

Finally, to examine the extent of the bias that would occur if there were multiple Us involved in the fetal selection process, we also estimated the value of $OR_{AY|S=1}$ and its 95% SI for each scenario in the presence of two and then three Us, where all Us were set to have the same prevalence and effect on selection. All simulations and analyses were performed in R (version 3.6.1; R Development Core Team). See simulation code and documentation at https://github.com/mleung-harvard/live-birth-bias-simulation and in the Supplemental Material, to explore the extent of potential biases with any selected parameters.

Results

The results of this simulation study on the bias in average $OR_{AY|S=1}$ are shown in Figure 2 and in Table S1. In the presence of collider-stratification with no interaction (M1), where both NO_2 exposure A and unmeasured variable U have independent causal effects on fetal loss and therefore selection S (i.e., OR_{AS} and OR_{US} were set to the prespecified selection effect, but $OR_{\{AU\}S}$ was set to 1), the bias was generally weak (Figure 2; Table S1). Selection effects of magnitudes 1.5 and 2.0 generated little to no bias on average across the three values of π_U, with $OR_{AY|S=1}$ ranging from 0.99 to 1. Only when the selection effects reached 3.0 did we see larger departures from the null (e.g., $OR_{AY|S=1}$ of 0.94 for π_U of 0.5), but these were still relatively weak, such that the 95% SI (i.e., the distribution of point estimates consistent with this mechanism) still included the null (Table S1). Examining the bias parameters $OR_{AU|S=1}$ and $\pi_{U|S=1}$, we observed that stronger selection effects in the total population yielded a lower $OR_{AU|S=1}$ (i.e., a stronger inverse association between A and U), but a smaller $\pi_{U|S=1}$ in the selected population (Figure 3; Table S2); that is, with stronger selection effects, both parameters deviate further from the underlying population parameter, where $OR_{AU|S=1}$ would be 1, and $\pi_{U|S=1}$ would be equal to π_U in the absence of bias.

For depletion of susceptibles (M2), where fetal loss is solely dependent on the interaction between NO_2 exposure A and unmeasured variable U (i.e., OR_{AS} and OR_{US} were set to 1, but $OR_{\{AU\}S}$ was set to the prespecified selection effect), the magnitude of bias was slightly stronger compared with those generated by M1 (Figure 2; Table S1). Unlike with M1, with M2, $OR_{AY|S=1}$ was consistently low, such that several 95% SI did not include the null (Table S1); for example, if the selection effects were 3.0 and 25% of the total population were exposed to U, then the observed OR for the NO_2 – ASD association would be 0.91 (95%

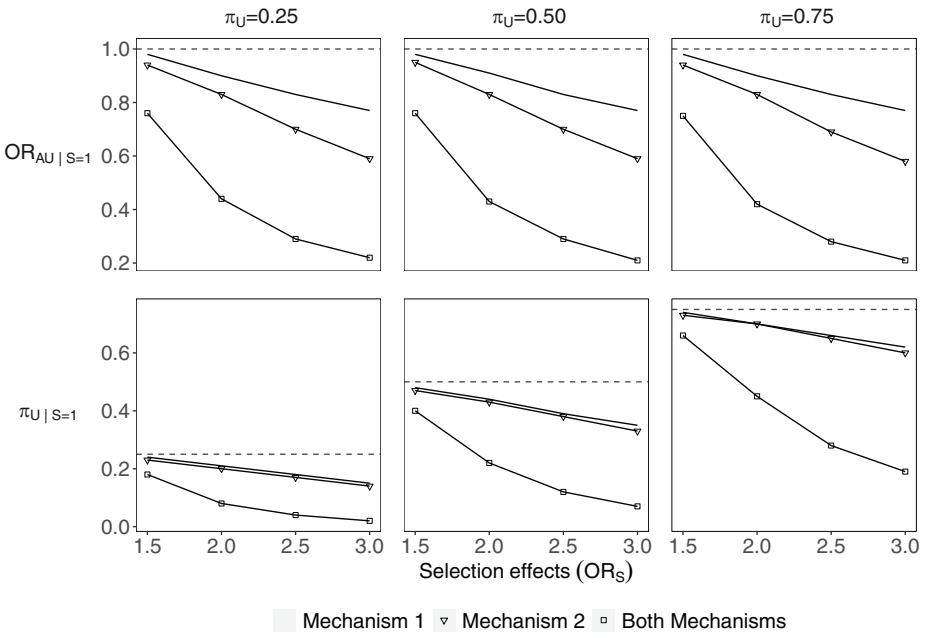

Figure 3. Bias parameters that drive live birth bias of OR_{AY} under different selection effects. Average bias parameters in the selected population with varying simulation inputs for the prevalence of the unmeasured risk factor U (π_U) and the magnitude of selection effects (OR_S) under two selection mechanisms and when they both co-occur with a single U, assuming a true null effect of nitrogen dioxide (NO_2; exposure A) on ASD (outcome Y). In the selected population (live births), $OR_{AU|S=1}$ is the association between A and U, and $\pi_{U|S=1}$ is the prevalence of U. Collider-stratification without interaction (Mechanism 1) occurs when A and U have independent causal effects on fetal loss, but with no interaction on the multiplicative scale ($OR_{\{AU\}S}=1$, and $OR_{AS}=OR_{US}=OR_{UY}=OR_S$). Depletion of susceptibles (Mechanism 2) occurs when A has a causal effect on fetal loss only in the subset of susceptible fetuses ($U=1$), but neither A or U have independent causal effects on fetal loss ($OR_{AS}=OR_{US}=1$, and $OR_{\{AU\}S}=OR_{UY}=OR_S$). Both mechanisms occur when A and U have independent causal effects on fetal loss, and with interaction on the multiplicative scale ($OR_{AS}=OR_{US}=OR_{\{AU\}S}=OR_{UY}=OR_S$). Each scenario was simulated 1000 times. Points represent the mean value of the bias parameter in each scenario. Dashed lines indicate the expected values (in the absence of live birth bias) for $\pi_{U|S=1}$ ($\pi_{U|S=1}=\pi_U$), and $OR_{AU|S=1}$ ($OR_{AU|S=1}=OR_{AU}=1$), which are the parameters in the selected population that drive the strength of live birth bias of OR_{AY}. See Table S2 for corresponding numeric data, including 95% SI. Note: ASD, autism spectrum disorder; OR, odds ratio; SI, simulation intervals.

SI: 0.85, 0.97). When selection parameters were relatively weak (i.e., OR_S of 1.5 and 2), corresponding values of $OR_{AU|S=1}$ (for the same π_U) deviated further from the null under M2 in comparison with M1 (Figure 3; Table S2). For example, when the selection effect $OR_{\{AU\}S}$ was set to 1.5 (and both $OR_{AS}=1$ and $OR_{US}=1$) and $\pi_U=0.75$, $OR_{AU|S=1}$ was 0.94 for depletion of susceptibles in compairson with 0.98 for M1.

When both mechanisms worked together (M1+2), where both A and U had independent causal effects and causally interacted on fetal loss (i.e., OR_{AS}, OR_{US}, and $OR_{\{AU\}S}$ were set to the prespecified selection effects), the magnitude of bias was usually strongest (Figure 2; Table S1). For example, if the selection effects were 3.0, and 50% of the total population were exposed to U ($\pi_U=0.50$), then the average OR for ASD by NO_2 among live births ($OR_{AU|S=1}$) would be 0.85 (95% SI: 0.74, 0.97) (Table S1). Even if we only changed the selection effects to 2.0, the observed OR was 0.90 (95% SI: 0.82, 0.99) (Table S1). Examining the bias parameters, both $OR_{AU|S=1}$ and $\pi_{U|S=1}$ deviated further from their corresponding population parameters under M1+2, in comparison with both M1 and M2 (Figure 3; Table S2). For example, when the prevalence of U was 0.75, and the selection effect were set to 3 ($OR_{AS}=3$, $OR_{US}=3$, $OR_{\{AU\}S}=3$), $OR_{AU|S=1}=0.21$, and $\pi_{U|S=1}=0.19$ for M1+2 in comparison with $OR_{AU|S=1}=0.77$ and $\pi_{U|S=1}=0.62$ for M1 ($OR_{AS}=3$, $OR_{US}=3$, $OR_{\{AU\}S}=1$), $OR_{AU|S=1}=0.58$, and $\pi_{U|S=1}=0.60$ for M2 ($OR_{AS}=1$, $OR_{US}=1$, $OR_{\{AU\}S}=3$).

In the presence of multiple Us, the bias is amplified with increasing number of Us, but the extent of the amplification differs by selection mechanism as shown in Figure 4 and in Table S3. For M1, the increase in bias is small overall, yielding small to moderate associations even in the presence of three Us. For example, when both OR_{AS} and OR_{US} for three Us were set to 1.5, the resulting $OR_{AY|S=1}$ were 0.99 for all values of π_U, compared with $OR_{AY|S=1}$ of 1 for all values of π_U when only one U was simulated. When both OR_{AS} and OR_{US} for three Us were set to 3.0, the resulting $OR_{AY|S=1}$ ranged from 0.87 to 0.90 across values of π_U, compared with $OR_{AY|S=1}$ of 0.94–0.95, when only one U was simulated. The amplification of bias with additional U parameters was stronger for M2 and strongest when both mechanisms co-occurred (M1+2). For example, when $OR_{\{AU\}S}$ for three $A-U$ interactions were set to 1.5 under M2 (OR_{AS} and OR_{US} set to 1), $OR_{AY|S=1}$ ranged from 0.94 to 0.97 in comparison with 1.0 for all values of π_U, when only one U was simulated. When OR_{AS}, OR_{US}, and $OR_{\{AU\}S}$ were set to 1.5 under mechanism M1+2 with three Us, $OR_{AY|S=1}$ ranged from 0.88 to 0.95, compared with 0.98 for all values of π_U when only one U was simulated. Bias increased under both mechanisms because the selection effects increased in magnitude, and the prevalence of U was high. The most extreme bias occurred when there were three Us under M1+2, OR_S was set to 3.0, and π_U was set to 0.75, resulting in an average $OR_{AY|S=1}$ of 0.51 (95% SI: 0.34, 0.73) for the NO_2-ASD association when the population was restricted to live births.

Discussion

In our simulations, we found that the magnitude of bias was generally weak for collider-stratification without interaction (M1), which is consistent not only with previous research on live-birth bias (Liew et al. 2015a) but also with existing literature that has focused on collider-stratification in other observational settings, such as the birth weight paradox (Hernández-Díaz et al. 2006), obesity paradox (Glymour and Vittinghoff 2014; Sperrin et al.

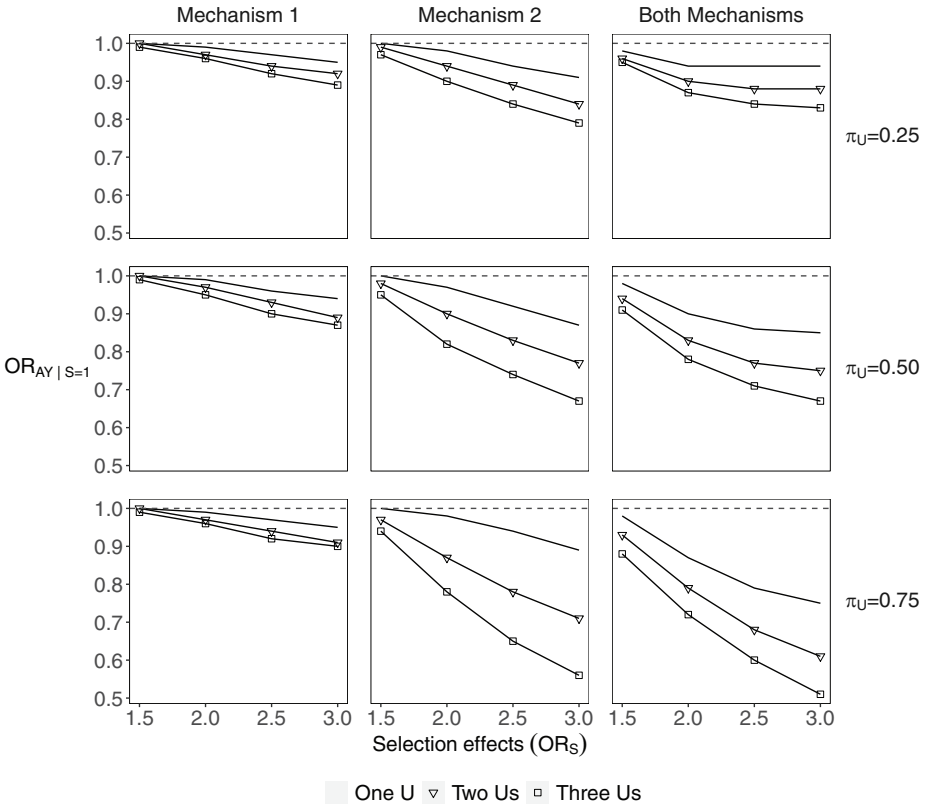

Figure 4. Live birth bias of OR_{AY} under different selection effects and different numbers of unmeasured risk factors for selection and the outcome. Average odds ratios for the association between nitrogen dioxide (NO_2; exposure A) and ASD (outcome Y) among live births $S=1$ ($OR_{AY|S=1}$) with varying simulation inputs for the prevalence of the unmeasured risk factor U (π_U) and the magnitude of selection effects (OR_S) under two selection mechanisms and when they both co-occur with one, two or three Us, assuming a true null effect of NO_2 on ASD. U is a vector that consists of ≤ 3 unmeasured factors (U_1, U_2, U_3), where input parameters were applied equally for each unmeasured factor; thus, all references to U henceforth applies to each of the unmeasured factors U_1, U_2, U_3. Collider-stratification without interaction (Mechanism 1) occurs when A and U have independent causal effects on fetal loss, but with no interaction on the multiplicative scale ($OR_{\{AU\}S}=1$, and $OR_{AS}=OR_{US}=OR_{UY}=OR_S$); Depletion of susceptibles (Mechanism 2) occurs when A has a causal effect on fetal loss only in the subset of susceptible fetuses ($U=1$), but neither A or U have independent causal effects on fetal loss ($OR_{AS}=OR_{US}=1$, and $OR_{\{AU\}S}=OR_{UY}=OR_S$); Both mechanisms occur when A and U have independent causal effects on fetal loss, and with interaction on the multiplicative scale ($OR_{AS}=OR_{US}=OR_{\{AU\}S}=OR_{UY}=OR_S$). Each scenario was simulated 1000 times. Points represent the mean $OR_{AY|S=1}$ in each scenario. Dashed lines indicate the true null effect of NO_2 on ASD ($OR_{AY}=1$) in the absence of live birth bias, where deviations from 1.0 quantify the magnitude of live birth bias. See Table S3 for corresponding numeric data, including 95% SI. Note: ASD, autism spectrum disorder; OR, odds ratio; SI, simulation intervals.

2016), and selection into genetic studies (Munafò et al. 2018), where much stronger and perhaps implausible effects are required to induce substantial bias (Greenland 2003; Smith and Vanderweele 2019). Thus, it is unlikely that collider-stratification without interaction alone can account for the observed association between pregnancy-wide NO_2 exposure and ASD in the original study (Raz et al. 2018b), because few simulated scenarios yielded ORs that were close to 0.77, the OR for NO_2 during pregnancy when mutually adjusted for postnatal exposure to NO_2 (Raz et al. 2018b). Although other factors could have been at play as well, depletion of susceptibles (M2) or both mechanisms operating simultaneously (M1+2) would be more likely to be able to account for the observed association in the original study all on their own, because the simulations under these scenarios consistently generated moderate to strong protective associations due to more extreme selection bias parameters among live births—particularly when multiple Us were present.

To better understand the differences between the two selection mechanisms with just a single unmeasured variable U, we also estimated the $A \rightarrow U$ association ($OR_{AU|S=1}$) and prevalence of U ($\pi_{U|S=1}$) in the selected populations, because the magnitude of bias ($OR_{AY|S=1}$) is constrained by these two parameters, and the effect of U on ASD (OR_{UY}). However, because OR_{UY} was the same across mechanisms in our simulations, any discrepancies in $A-Y$ bias are driven by both $OR_{AU|S=1}$ and $\pi_{U|S=1}$. Here, M1 generally yielded weaker $OR_{AU|S=1}$ but similar $\pi_{U|S=1}$ in comaprison with M2, which explains why M1 produces a weaker bias compared with M2. When both mechanisms co-occur (M1+2), $OR_{AU|S=1}$ is lower (i.e., A and U are more strongly negatively associated) than either M1 or M2; this is unsurprising given that the effects of A and U on selection are "super-additive" under M1+2, in that the contributions of A and U together exceed the sum of their contributions when A and U are considered separately, as shown in Equation 1. Furthermore, $\pi_{U|S=1}$ is also lower under M1+2, however, this does not necessarily generate more bias because, similar to the magnitude of bias due to confounding (Walker 1991), bias is maximized when $\pi_{U|S=1}=0.50$ ($\pi_{U|S=1}$ that is close to 0 or 1 actually reduces bias, because this is akin to conditioning on or stratifying by variable U). Thus, when $\pi_U \leq 0.5$, there exists a tension between the strength of $OR_{AU|S=1}$ and the distance of $\pi_{U|S=1}$ from 0.50, because stronger selection effects reduced $\pi_{U|S=1}$ (i.e., it moves further away from 0.50), such that it could offset the bias generated by the stronger $OR_{AU|S=1}$. For example, when $\pi_U=0.25$ and $OR_S=3.0$,the bias under M1+2 was weaker than under M2 ($OR_{AY|S=1}=0.94$ under M1+2 and $OR_{AY|S=1}=0.91$ under M2) because despite the stronger $OR_{AU|S=1}$ ($OR_{AU|S=1}=0.22$ under M1+2 and $OR_{AU|S=1}=0.59$ under M2) $\pi_{U|S=1}$ was further away from 0.50 ($\pi_{U|S=1}=0.02$ under M1+2 and $\pi_{U|S=1}=0.14$ for M2).

On the other hand, when $\pi_U = 0.75$, stronger selection effects strengthened $OR_{AU|S=1}$, and lowered $\pi_{U|S=1}$ closer to 0.50 (except when $OR_S = 3.0$ under M1+2, where $\pi_{U|S=1} = 0.19$), such that both bias parameters worked in concert to increase the bias in the overall $OR_{AY|S=1}$ association.

Evaluating the range of plausible parameters for simulation inputs is important for bias analyses. With a single unmeasured variable U, neither M1 nor M2 produced associations near the observed OR of 0.77 from the original study (Raz et al. 2018b). On the other hand, when both mechanisms operate together (M1+2) and there is just a single unmeasured variable U, not only do the selection effects need to be quite strong, but also U needs to be relatively common in the population to yield this observed OR. For example, an OR_S of 3.0 and π_U of 0.75 yielded an observed association of 0.75 (95% SI: 0.64, 0.89) in our simulations. Thus, with a single U, not only are there very few scenarios that could produce the observed estimate, but the magnitude of the input parameters that could potentially generate the bias strains credibility. That is, although it is perhaps plausible that one of the selection effects is that large, it seems unlikely that all three are. Therefore, strong bias is more likely under either M2 or M1+2 when U is a composite of uncontrolled variables (as well as those that have been controlled for, just imperfectly), because the OR_S would only need to be between 1.5 and 2.0 to generate a bias of similar magnitude. With selection effects of 2.0, and $\pi_U = 0.75$ for each U, the $OR_{AY|S=1}$ was 0.87 and 0.78 under M2 when there were two and three Us, respectively; whereas, with the same input parameters, the $OR_{AY|S=1}$ was 0.79 and 0.72 under M1+2 when there were two and three Us, respectively. Even if these unmeasured factors were just as strongly associated with S and Y, but were less prevalent in the population, the mean $OR_{AY|S=1}$ is only slightly attenuated. For example, under the same selection effects, but when $\pi_U = 0.50$ for each U, the $OR_{AY|S=1}$ was 0.90 and 0.82 under M2 when there were two and three Us, respectively, and the $OR_{AY|S=1}$ was 0.83 and 0.78 under M1+2 when there were two and three Us, respectively.

Potential candidates for U include prenatal stress (Bercum et al. 2015; Beversdorf et al. 2005; Bruckner et al. 2016; Brunton 2013; Class et al. 2014; Coughlan et al. 2014; Dean et al. 2015; Kinney et al. 2008a, 2008b; Li et al. 2012; Nepomnaschy et al. 2006; Plana-Ripoll et al. 2016; Roberts et al. 2013, 2014; Wainstock et al. 2013; Walder et al. 2014; Wisborg et al. 2008), maternal smoking (Caramaschi et al. 2018; Jung et al. 2017; Marufu et al. 2015; Pineles et al. 2014), genetic factors (Grove et al. 2019; Page and Silver 2016; Risch et al. 1999), and environmental stressors such as endocrine-disrupting chemicals (EDCs) (Jensen et al. 2015; Kalkbrenner et al. 2014; Krieg et al. 2016; Pelch et al. 2019). Many of these associations have been reported to be in line with or stronger than an OR_S of 1.5–2.0, and the collective exposure to these factors (or just a subset) in the population is likely not uncommon. For example, maternal smoking during pregnancy (any vs. none) has been associated with an OR of 1.47 for stillbirth (Marufu et al. 2015) and an OR of 1.56 for autism (Caramaschi et al. 2018). Furthermore, EDCs such as polychlorinated biphenyls (PCBs) have been associated with pregnancy loss with ORs ranging from 1.6 to 2.52, depending on the type of PCB, when comparing those accidentally exposed vs. those unexposed to accidental contamination of rice oil during the Yusho incident in Japan in 1968 (Krieg et al. 2016; Tsukimori et al. 2008). PCBs have also been associated with increased odds of autism, where a prior study reported ORs ranging from 1.20 to 1.97, depending on the type of PCB, when comparing the highest to the lowest quartile of exposure (Bernardo et al. 2019). Although we identified these Us for our illustrative example of NO_2 and ASD, they are also relevant for the estimation of the effects of any exposure during pregnancy that has the potential to cause loss and ASD. Furthermore, an OR_{AS} of 1.5 to 2.0 is also plausible for the effects of NO_2 on loss. Although past studies have reported ORs ranging from 1.04 to 1.27 for the association between NO_2 (typically per 10 ppb) and pregnancy loss (Grippo et al. 2018), these are likely biased downward because only a subset of pregnancy losses come to medical attention and can be studied. That is, early pregnancy loss, which has been estimated to be around 20%–30% (Wilcox et al. 1988), are typically not observed, such that NO_2-induced loss early in pregnancy would go undetected, and the resultant association would underestimate the true harmful effect of NO_2 on pregnancy loss. Because our simulation code is available online, we encourage other investigators to evaluate the potential bias arising from live-birth bias with input parameter values that are relevant to their own research.

Although our simulations could generate the magnitude of the protective effect reported from the original nested case–control study using a range of plausible input parameter values, they are simplified depictions of potential causal structures and, therefore, should not be directly compared with estimates from analyses using real data. For example, for simplicity, we assumed no confounding of the exposure effects, no loss to follow-up among live-born children, no measurement error, and no seasonal or time trends in the exposure or outcome. It is unlikely that all these assumptions would hold in a real analysis. The potential bias in the original nested case–control study may actually be a net downward bias (assuming that exposure to NO_2 during pregnancy is not neuroprotective) arising from a combination of residual and/or unmeasured confounding, selection bias due to nonrandom attrition between birth and ASD assessment (although such selection would be subject to the same issues we describe here for live-birth bias), exposure measurement error (which typically biases the estimate toward the null), outcome misclassification, and model misspecification (e.g., imperfect control for seasonal trends) in addition to live-birth bias. However, the simplicity of our current simulation study is also its strength, in that in our simulations we can isolate and fully identify the bias due to the specific fetal selection mechanism. Furthermore, as prior knowledge of the magnitude and sign of the selection effects (OR_{AS}, OR_{US}, $OR_{\{AU\}S}$, OR_{UY}) is limited because pregnancy loss is a challenging outcome to study (Finer and Zolna 2016; Wilcox et al. 1988), we set these ORs to be equal in our simulations for simplicity, but presumably similar associations could be seen with some OR lower and others higher. Along similar lines, we ran our simulations under the null for simplicity, which is sufficient to evaluate the magnitude of bias, because it does not depend on the effect of NO_2 on ASD. For example, if we observe an $OR_{AY|S=1}$ of 0.75 for a given selection mechanism under the null, then a true effect of $OR_{AY} = 1.33$ (i.e., the inverse of 0.75) would be rendered null by this selection mechanism. Finally, we also assumed that exposure groups are exchangeable in the total population of all conceptions (e.g., conceptions are not affected by selection processes induced by preconception exposures). However, this exchangeability may not be the case because there are likely selection processes that influence fertility (i.e., the likelihood of conception). Excluding women of reproductive age who are trying but are unable to conceive (because pregnancy is a requirement to study exposures during pregnancy) may lead to biased exposure–health effects in the set of actual conceptions, which differs from the total population of intended conceptions. This bias would act through mechanisms similar to those that we address in this paper's simulations and therefore could amplify live-birth bias in an analysis with real data (Figure S1).

Here, we show that live-birth bias under plausible simulation parameters can lead to associations of NO_2 and ASD that are biased downward, where the largest bias occurs when both M1 and M2 both operate simultaneously (i.e., M1+2). This bias may explain the inconsistent body of literature (Flores-Pajot et al. 2016; Lam et al. 2016; Raz et al. 2018b; Weisskopf et al. 2015; Yang et al. 2017), where truly adverse effects may appear not as harmful, null, or even protective. Although we used NO_2 and ASD for our illustrative example, this bias can extend to other studies relevant to fetal programming (Barker 2004), which can limit the identification of harmful prenatal exposure effects and prevent the development of interventions during pregnancy aimed at promoting better health. For example, it is possible that live-birth bias can also explain the unexpected negative associations between prenatal exposure to perfluoroalkyl substances with ASD (Hertz-Picciotto et al. 2008) and attention-deficit/hyperactivity disorder (Fei and Olsen 2011; Liew et al. 2015b; Ode et al. 2014; Stein et al. 2013).

To rule out live-birth bias as a threat to internal validity, we would need to show that the exposure in question does not affect selection (i.e., fetal loss); that is, if we find that exposure does not affect selection, either independently or in conjunction with another risk factor for fetal loss, then the association with the outcome cannot be biased through this mechanism. If, on the other hand, exposure is associated with selection, then to potentially mitigate or eliminate this bias, we would need to collect information on U (something we would need to plan for in the study design phase) and adjust for it in the analysis. Last, if there is reason to believe that there are no common causes of selection and the outcome, then there would be no live-birth bias, even if the exposure affects selection (although this is impossible to verify in practice). It would still be worthwhile to quantify the effect of exposure on selection, because it gives us insight into the change in the potential number of losses and the child outcome (when considered jointly with its effect on the outcome) if we were to intervene to set exposure to another level. All of these analyses require estimating the effects on selection, which is no simple feat; however, new approaches for studying pregnancy loss without needing to enumerate the population at risk (i.e., all conceptions) (Kioumourtzoglou et al. 2019) makes such an undertaking less daunting. Thus, our study findings highlight the need for cautious interpretations of studies of the effects of prenatal exposures on postnatal outcomes and for more investment into research on the determinants of pregnancy loss.

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